REMARKS/ARGUMENTS

The Advisory Action mailed May 26, 2004 indicated that the amendments to previously pending claims 13, 16, 21-23, 30, 34 and 36 would be entered for purposes of appeal. Those claims are re-presented above in conjunction with the accompanying Request for Continued Examination (RCE). The correspondence between the previous claims and new claims 37-61 above are shown in the following table:

Previously pending claim	New claim
13	37
16	45
21	38
22	43
23	46
30	41
34	42
36	39

New claims 40, 44, and 47-61 have not been previously presented. Support for these claims, especially claims 40 and 44 is found at least in the claims as previously presented. Support for claims 47-48, 53-55 and 60 is found at least on page 30, ¶105 of the instant specification; for claims 49 and 56, page 12, ¶44; for claims 50-51 and 57-58, page 17-18, ¶59-60, and page 20, ¶71; for claims 52 and 59, page 28, ¶100; and for claim 61, page 22, ¶77.

No new matter has been presented, and entry of the above amendment to the claims is respectfully requested.

Telephonic Interview of May 4, 2004

Applicants believe that the substance of the telephonic interview of May 4, 2004 is of particular relevance to the instant application and the pending claims. The interview took

place between Examiner Kam and the undersigned with Andrew Cubitt of X-Ceptor Therapeutics, Inc., the assignee of record in the instant application. The Advisory Action mailed April 20, 2004 was discussed during the interview.

Applicants sought to clarify the situation with respect to the claimed invention and the rejection of record under 35 U.S.C. § 112, first paragraph. In particular, Applicants pointed out that the invention was directed to the use of LXR agonists based on their ability to affect glucose metabolism. This is in contrast to much of the Examiner's stated positions to date, which focused on the use of LXR agonists in relation to lipid metabolism. Additionally, Applicants pointed out that the Examiner's emphasis on an alleged lack of "structure/function" relationship was misplaced because LXR agonists of various structures are known and it is the functionality of being an LXR agonist, rather than any particular compound structure, which is the basis for the claimed invention's ability to affect glucose metabolism. Additionally, Applicants asserted that no undue experimentation is necessary to determine appropriate dosages to use.

Further discussion of Applicants' position are provided below, which represents a complete response to the last Office Action mailed January 6, 2004.

Objections to Claims

Claims 16 and 23 (now claims 45 and 46) were objected to because the claims allegedly referred to non-elected additional active agents. Applicants respectfully traverse the objection, but have presented claims 45-46 to reduce issues and to expedite the allowance of the present application. Applicants accordingly request withdrawal of the objection. Applicants reserve the right to pursue non-elected subject matter in a continuing application without prejudice.

Issue under 35 U.S.C. §112 First Paragraph

Previous claims 13, 16, 17, 21-23, 30, 31, 34 and 36 were rejected under 35 U.S.C. §112, first paragraph as allegedly not enabled such that a skilled artisan could make and/or use the invention commensurate in scope with the claims. The Examiner alleges (see

page 4 of the Office Action) that while the specification is enabling for a method of treating diabetes type II comprising administering a specific LXR agonist, (compound 1), the specification does not reasonably provide enablement for a method for treating, or reducing the risk of developing or recurrence of diabetes, with the disclosed compound, or treating type II diabetes wherein the structure of the LXR agonist is not defined.

Additionally, the Advisory Actions mailed April 20 and May 26 2004 assert that undue experimentation is needed to use LXR agonists of structures other than compound 1 as used in the Example section of the instant application at appropriate dosages; and that the claims encompass the use of unspecified LXR agonists.

Applicants respectfully traverse the rejection on the grounds that the currently pending claims are fully enabled by the present specification and the knowledge of the skilled practitioner. Accordingly, no *prima facie* case of non-enablement is present.

As an initial matter, Applicants point out that claims 17 and 31 are no longer pending because the remaining claims are better tailored to currently contemplated, commercially relevant, embodiments of the invention. The cancellation of claims 17 and 31 is thus not in acquiescence to the instant rejection. Additionally, Applicants point out that new claims 53 and 60 are directed to methods comprising the use of compound 1. Accordingly, claims 53 and 60 should not be subject to the instant rejection.

Additionally, and as noted above, the instant invention is based on the discovery of the effect of LXR agonists on glucose metabolism. Thus, Applicants respectfully submit that the Examiner's reliance on information regarding LXR agonist activity in relation to lipid metabolism is misplaced. The fact that LXR agonists have been defined or characterized in the past in relation to lipid metabolism does not negate or alter the discovery that the agonists may be effectively used to decrease hyperglycemia and insulin resistance as provided by the instant disclosure and application.

With respect to the possible concern and emphasis regarding the scope of the claims, Applicants point out that the fact that the claims encompass the use of "LXR agonists" without recitation of particular structures raises **no** issue of undue experimentation. As noted during the telephonic interview and in the response filed October 16, 2003 (mailed October 13,

2003), LXR agonists of various structures are known (see pages 9 and 10 of the response filed October 16, 2003). The allegation that enablement is limited to particular structures which function as LXR agonists is misplaced because the agonists are claimed, and act, by virtue of their ability to function as an LXR agonist. It is the use of this activity, rather than any particular structure, which is claimed as the invention. Since it is the activity that supports the use of the agonists in relation to glucose metabolism, it is entirely proper (and permitted[1]) to claim the agonists by function rather than structure. Moreover, and as the Examiner no doubt appreciates, enablement does not require the recitation of that which is known in the art, such as the identities and structures of compounds already known as LXR agonists.

Additionally, and to assist the Examiner in advancing the prosecution of the instant application, attached is a copy of Stulnig *et al.* ("Liver X receptors downregulate 11β-hydroxysteroid dehydrogenase type 1 expression and activity" Diabetes, 51:2426-2433, 2002). While this article was published after the filing date of the instant application, it may nevertheless be used to support Applicants' position that LXR agonists can be used to decrease hyperglycemia, and thus treat diabetes and insulin resistance. The article provides a possible mechanism by which LXR agonists act.

Stulnig *et al.* describe the effects of multiple LXR agonists *with distinct structures* as able to downregulate 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD-1) expression. Stulnig *et al.* note that 11β-HSD-1 "appears to be causally linked to the development of type 2 diabetes and the metabolic syndrome" (see abstract). They further suggest that LXR agonists may "have beneficial effects on the metabolic control in patients with type 2 diabetes" (see page 2431, right column, end of second full paragraph).

In particular, Stulnig *et al.* demonstrate that the down regulation is caused by addition of the synthetic LXR agonist T0901317 as well as two naturally occurring LXR agonists, 22(R)-hydroxycholesterol and 20(S)-hydroxycholesterol (see Figure 3 and Figure 7A), to the cells. The T0901317 agonist is identical to that disclosed in Cao *et al.* (J. Biol. Chem.

[1] See MPEP 2173.05(g) and the cases cited therein.

278(2):1131-1136, 2003 as cited in the previous response filed May 6, 2004)) [2] Stulnig *et al.* further suggest that LXR agonists have "the potential to exert positive effects on insulin sensitivity." (see pages 2429-2430, bridging paragraph).

The fact that two independent groups of researchers in two countries come to the same conclusion regarding the ability to use structurally different LXR agonists in relation to diabetes clearly shows that there would have been no undue experimentation at the time of the invention to use LXR agonists of any structure in the methods of the invention as claimed.

Based on the foregoing, and as previously presented by Applicants, there is simply no objective reason to doubt the fact that LXR agonists may be used to treat diabetes by decreasing hyperglycemia and/or reducing insulin resistance. Accordingly, there is no objective reason to limit the claims to only treatment of type II diabetes with a single compound.

As for the reliance on an alleged need to define dosages for the use of additional LXR agonists, Applicants respectfully submit that no issue of undue experimentation is present. As noted during the telephonic interview, it is well settled that undue experimentation is not the absence of experimentation.[3] Undue experimentation is also not the possible need for experimentation to find a previously unknown answer. On the other hand, it is also well settled that routine and repetitive experimentation is not undue. Applied to the situation of additional LXR agonists, Applicants respectfully point out that no more than routine or repetitive experimentation is needed to determine dosages for various agonists. This is supported by the dose dependent effects on plasma glucose levels shown by Cao *et al.* and as noted above. Additionally, Figure 15 of the instant application demonstrates how routine it is to determine effective dosages for reducing plasma glucose levels. A given LXR agonist, such as 22(R)-hydroxycholesterol or 20(S)-hydroxycholesterol, at a give dosage can be administered and compared to a control to observe the effects on plasma glucose levels over time (see Figure 15). Applicants respectfully submit that a person skilled in the art can thus experiment with a variety

[2] Applicants regret any confusion that may have been caused by the previous error in asserting a difference between instant compound 1 and the T0901317 agonist.

[3] *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).

of LXR agonists at a variety of dosages to identify suitable dosages without undue experimentation.

In light of the foregoing, Applicants strongly submit that no issue of undue experimentation, and thus lack of enablement, exists with respect to previous claims 13, 16, 21-23, 30, 34 and 36 or the currently pending claims. Accordingly, this rejection should be withdrawn and the claims indicated as allowable.

Form PTO-1449

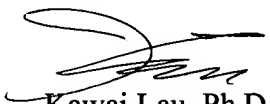
The Cao *et al.* reference was previously provided in the instant application, and the Stulnig *et al.* reference is provided herewith. Applicants have included a form PTO-1449 listing both of these references and request that an initialed copy of the form be returned with the next communication to indicate that the references have been made of record.

Conclusion

Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is urged.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 858-350-6151 .

Respectfully submitted,



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